

Initiated 7/1/56

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 EAST FORTY SECOND STREET NEW YORK 17, N. Y.
RENEWAL

128R1

Application For Research Grant

Date: January 24, 1957

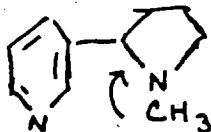
1. Name of Investigator: 1. Paul S. Larson
2. H. B. Haag
3. Herbert McKennis, Jr.
2. Title: 1. Professor of Pharmacology
2. Professor of Pharmacology
3. Professor of Research Pharmacology
3. Institution
& Address: Medical College of Virginia
Richmond 19, Virginia

4. Project or Subject:

Enzymatic Transformations of Nicotine and Related Compounds.
(Continuance application for period of July 1, 1957 -
June 30, 1958)

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

In the enclosed half-yearly progress report it will be seen that the metabolism of nicotine has been considered to fall into three categories. Current work is concerned almost exclusively with the "cotinine pathway" of nicotine metabolism. Methods have been developed for the synthesis of compounds of interest for this pathway, and methods have been devised for the isolation and separation of the compounds. Currently work on the metabolism of the intermediates (actual and postulated) is in progress. It is anticipated that during the months that follow substantial further progress will have been made. It is then planned to investigate the nature of the physiological processes involved in attack of the pyrrolidine ring on the opposite side of the ring as indicated below:



While the ring cleavage currently being studied leads to the development of compounds which appear to be devoid of nicotine-like action, it can be seen that many of the products from ring attack and cleavage (as shown above) may resemble nicotine or perhaps some of the pressor amines in their action. Plans would include a systematic study of methods for isolation and identification of products which may be anticipated from this general type of biological degradation. Attempts will be made to correlate the occurrence of 3-pyridylpropyl ketone in fermented tobacco to metabolic pathways deemed capable of producing the same compound in higher organisms. The improved methods for chemical synthesis of nornicotine and nicotine which have arisen from work accomplished during the first six months of the current grant will make possible new applications of C^{14} to the study of nicotine metabolism as herein projected.

1003541359

6. Budget Plan: (Second Year)

Social Security	\$ 189.00
Salaries	13,700.00
Expendable Supplies	4,000.00
Permanent Equipment	2,800.00
* Overhead (10%)	2,103.90
Other (Travel)	350.00
Total	\$23,142.90

7. Anticipated Duration of Work:

Two years

8. Facilities and Staff Available:

General pharmacologic and biochemical equipment. Lardy type Warburg apparatus, refrigerator centrifuge, C^{14} counting equipment (Libby anticoincidence counter, nuclear instrument gas flow counter with automatic sample changer) paper chromatographic equipment, polarimeter, green house facilities for growing C^{14} labelled plants.

Staff: full time: Lennox B. Turnbull, Ph.D., Edward R. Bowman, M.S.,
part time: Dr. Paul S. Larson, Dr. H. B. Haag, Dr. Herbert McKennis, Jr.

9. Additional Requirements:

What, if any, will depend upon how the project develops.

10. Additional Information (Including relation of work to other projects and other sources of supply):

The breakdown of permanent equipment items is as follows:

2 Fraction Collector (with set of siphons)	\$1,950.00
1 Unterzaucher oxygen determination apparatus	850.00

The fraction collectors are required to relieve personnel from the time-consuming manual collection of samples.

The oxygen determination apparatus is required to make possible determination of the oxygen content of some of the pyridine derivatives. The apparatus also can be used in determining the source and biochemical stability of oxygen intermediates (through use of O^{18}). Facilities for determination of oxygen are very sparsely distributed throughout the country and are not generally available for outside work.

The breakdown for salaries is as follows:

L. B. Turnbull, Ph.D.	\$8,000.00
E. R. Bowman, M.S.	5,700.00

Paul S. Larson
H. B. Haag

Signature: Herbert McKennis, Jr.
Director of Project

W. T. Tompkins
Business Officer of the Institution

Comptroller